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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/513,997	02/26/2000	John J. Harrington	5817-7Q	9509

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EXAMINER
SHUKLA, RAM R

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 04/25/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/513,997	HARRINGTON ET AL.	
	Examiner	Art Unit	
	Ram R. Shukla	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 April 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *83-88,92,100-103,106 and 107* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *83-88,92,100-103,106 and 107* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *2,9,14* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Continued Prosecution Application

1. The request filed on 2-25-02 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 09/513,997 is acceptable and a CPA has been established. An action on the CPA follows.

2. Claims 83-88, 92, 100-103, 106, and 107 are pending in the instant application.

3. The 112 second paragraph rejection of claims 106 and 107 has been withdrawn.

4. The ref AT25 in the IDS filed 2-12-01 has been considered but a line has been crossed through it because it does not have a publication date and cannot be published.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 107 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention for reasons of record set forth in the previous office action of 8-23-01.

37 CFR 1.118 (a) states that "No amendment shall introduce new matter into the disclosure of an application after the filing date of the application".

Response to Arguments

Applicant's arguments filed 4-17-02 have been fully considered but they are not persuasive. Applicants have argued that claim 107 is dependent on cancelled claim 82 and step d of claim 82 is drawn to screening. However, these arguments are not persuasive because claim 82 was drawn to a method of producing an expression product of an endogenous gene in vivo whereas claim 107 is drawn to a method for detecting and the two methods are not same. Next applicants direct to different parts of the specification (pages 7-9, 13, 16, 17, 29 and 35) for written support for claim 107, however, none of the indicated sections of the specification disclose any such method.

Accordingly, the rejection is maintained.

7. Claims 83-88, 92, 100-103, 106, and 107 are rejected under 35 U.S.C. 112, first paragraph as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention for reasons of record set forth in the previous office actions of 2-14-01 and 8-23-01 and as discussed below.

In addition to the issues raised in the above mentioned office actions, it is noted that the vector recited in claims 106 and 107 comprise only a transcriptional regulatory signal, however, the distinct feature of the vector taught in the instant application is that it comprises a splice donor site and when incorporated into the genome of a cell by non-homologous recombination, a transcript produced under the control of the transcriptional regulatory signal and comprising the splice donor site of the vector and a splice acceptor site of an endogenous gene is spliced to produce a protein from the exon(s) of the endogenous 3' to the splice acceptor site where splice occurred. The specification does not teach that any vector comprising just a transcription regulatory sequence will function to over express or activate protein production from an endogenous gene.

Next, the only description of an in vivo method is usually a single sentence that says the cells can be used for in vivo expression, such as on page 7, line 8-9. The specification does not provide any specific guidance or description as to how the claimed methods would have been carried out. The specification does not teach or provide any guidance as to how the cells will be maintained in vivo into an animal, what will be appropriate conditions for over expression etc. Additionally, the claimed invention recites portions of genes that encode protein, again the specification does not provide any specific description as to how an artisan will practice the methods in which portion of proteins are produced. It is emphasized that the specification does not teach any specific teaching for carrying out any in vivo method. Rather, applicants have argued for support in the art and that an artisan would be able to do it. However,

Response to Arguments

Applicant's arguments filed 4-17-02 have been fully considered but they are not persuasive. With respect to the issue that the specification only describes therapy as the only utility, applicants have argued that cell therapy is only an example and that non-therapeutic utility of protein production from a cell introduced into an animal is well established (readily apparent). In support of their arguments they have provided a declaration by the inventor.

The declaration by the inventors has been full considered, however, it has not been found persuasive to obviate the rejection. In the declaration, the inventor states that the articles by Brodeur et al (J Immunol. Methods 71:265-272, 1984), Kints et al (J Immunol. Methods 118: 241-245, 1989) and Stewart et al (J Immunol. Methods 119: 269-275, 1989) teach a method for introducing hybridomas into mice and rat to produce large quantities of antibodies. However, these arguments are not persuasive because the claimed method is not for introducing hybridomas and producing antibodies in mice or rat. Therefore, these arts do not provide support that the readily apparent utility for the claimed invention is for introducing hybridomas and producing antibodies. The inventor

further argued that the specification in 08/941,223, 09/276820 disclose using hybridomas to express endogenous genes. Since it is not clear how the sections of the '223 and '820 applications are related to the instant application, the relevance of this argument cannot be determined. Even if the relevant sections of the instant application were identified, the argument is irrelevant because the claimed method is not same as introducing hybridomas and producing antibodies.

Next, the inventor, in the declaration, cites patent US patents 5,733,761 and 5,641,670 (Treco et al) and other applications related to this and states that the patents teach production of protein in vivo and that the cells introduced into animal are useful for eliciting antibody production or meat and dairy production. It is noted that the method of US patent 5,733,761 and other related patents, PCT applications and WO documents can not be used to support utilities for the instant application because the two methods are fundamentally different. In the cited Treco patents and documents, expression of a certain endogenous gene is activated, in contrast to the method of the instant application where the expression of any gene is activated and one may or may not produce a full-length protein.

Next the inventor discusses the Shaw et al (JEM 185:1711-1714, 1997) which describes local delivery of IL-4 by retrovirus transduced T lymphocytes to experimental autoimmune encephalitis. Again the article of Shaw et al is not related to the instantly recited invention because Shaw at al uses cells that have been transduced with a vector that expresses IL-4 and the vector and the method of Shaw et al has vector are not even remotely related. Again the inventor refers to sections of other applications '223 and '820 and not to the instant application, however, the discussion is irrelevant because the method of Shaw and that of the claimed invention are not related.

Next, the inventor discusses Chen et al (The J of Neuroscience 15:2819-2825, 1995) that describes somatic gene transfer of NGF where primary fibroblasts modified to secrete NGF were implanted into NBM of memory impaired rats. Again the method recite in the instant application is not related to the method of Chen because cells in Chen were modified by introducing retroviral vectors expressing

NGF cDNA. In fact, the method of Chen is to ex vivo cell therapy, which is not enabled for the instant application.

Next, the inventor, discusses Garver et al (Science 237: 762-764, 1987), which again is directed to ex vivo gene therapy, which is not enabled for the instant application. Likewise, the art of McNiece et al (Leukemia Res. 9:1069-1074, 1985) uses tumor cells (WEHI-3 cells), which again does not have any similarity to the cells produced in the instant application. Ishihara et al also teach injection of tumor cells to rats for characterization of protease. Again, the cells used by Ishihara et al (Invasion Metastasis 6:225-245, 1986) are tumor cells and do not have any thing common to the cells of the instant application.

Finally, the article of Bronson et al (PNAS 93:9067-9072, 1996) is also not relevant because that in this case the vector had the sequence encoding Bcl2 compared to the vector of the instant application which does not have any exogenous encoding sequences.

In summary, while the inventor, in the declaration, asserts the specification teaches introducing cells expressing a protein of interest into an animal, none of the arts they had supplied in the declaration describe a cell similar to their cell, therefore, the utility described for the different types of cells (discussed by the inventor in the declaration) can not provide readily apparent utility for the cells of the instantly claimed invention.

On pages 12, applicants have argued that the specification teaches the claimed method to produced isolation and purification of protein produced in an animal by the cells of the invention. It is reiterated that the specification except for single sentences regarding in vivo method does not provide how would an artisan of skill have practiced the claimed method. It is noted that since the cells used in the claimed invention are not related or similar to any other cells that the applicants have discussed, the method used in these other unrelated art cannot be used to support the enablement or other readily apparent utilities. Applicants have failed to provide any evidence where in the specification how to make and use the claimed methods have been described. Pages 7-9, 13, 16, 17, 29 and 35 of the 08/941223 provide cursory statements, such as "Alternatively the cells can be allowed to

express the desired gene product *in vivo*" (page 7, lines 8-9); "The cells can be used to provide desired amounts of a gene product in vitro or in vivo, The gene product can then be isolated and purified if desired. It can be purified by cell lysis or from growth medium (as when the vector sequence contains a secretion signal sequence)" (page 8, lines 14-17). Applicants are arguing that such statements provide enabling disclosure for the claimed methods, however, it is not clear how an artisan of skill would have been able to practice the claimed method by following these cursory general statements.

In conclusion, it is emphasized that the specification does not teach any specific teaching for carrying out any in vivo method. Rather, applicants have argued for support in the art and that an artisan would be able practice by following what is known in the art. However, the specification has to teach the invention not the art.

Court states, "It is true, as Genentech argues, that a specification need not disclose what is well known in the art. See, e.g., Hybritech Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1385, 231 USPQ 81, 94 (Fed. Cir. 1986). However, that general, oft-repeated statement is merely a rule of supplementation, not a substitute for a basic enabling disclosure. It means that the omission of minor details does not cause a specification to fail to meet the enablement requirement. However, when there is no disclosure of any specific starting material or of any of the conditions under which a process can be carried out, undue experimentation is required; there is a failure to meet the enablement requirement that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art. It is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement." (See Brenner v. Manson, 383 U.S. 519, 536, 148 USPQ 689, 696 (1966))

8. The 102 and 103 rejections have been withdrawn in view of the applicant's arguments.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 83-88, 92, and 100-103 remain provisionally rejected and claim 106 is provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 81, 83-88, 92, and 100-103, respectively, of copending Application No. 09/479,122 for reasons of record set forth in the previous office action of 8-23-01. Although the conflicting claims are not identical, they are not patentably distinct from each other because rejected claims 83-88, 92, 100-103, and 106 are embraced by claims 81, 83-88, 92, and 100-103 of the copending application.

Claim 100 remains provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 88 of copending Application No. 09/481,375; claim 60 of copending Application Nos. 09/455,659 and 09/513,575; and claim 59 of copending Application Nos. 09/479,123 and 09/513,574 for reasons of record set forth in the previous office action of 8-23-01. Although the conflicting claims are not identical, they are not patentably distinct from each other because rejected claim 100 is embraced by claim 88 of copending application 09/481,375, and because rejected claim 100

embraces the recited claims of copending applications 09/455,659, 09/513,575, 09/479,123, and 09/513,574.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

9. Applicants did not respond to these double patenting rejections in their preliminary remarks filed 4-17-02

10. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ram R. Shukla whose telephone number is (703) 305-1677. The examiner can normally be reached on Monday through Friday from 7:30 am to 4:00 p.m. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached on (703) 305-4051. The fax phone number for this Group is (703) 308-4242. The after-final fax number is (703) 87209307. Any inquiry of a general nature, formal matters or relating to the status of this application or proceeding should be directed to the William Phillips whose telephone number is (703) 305-3413.

Ram R. Shukla

RAM R. SHUKLA, PH.D
PATENT EXAMINER

Ram R. Shukla, Ph.D.
Primary Examiner
Art Unit 1632